Human neural stem cell tropism to metastatic breast cancer.

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Public Summary:
ABSTRACT Metastasis to multiple organs is the primary cause of mortality in breast cancer patients. The poor prognosis for patients with metastatic breast cancer and toxic side effects of currently available treatments necessitate the development of effective tumor-selective therapies. Neural stem cells (NSCs) possess inherent tumor tropic properties that enable them to overcome many obstacles of drug delivery that limit effective chemotherapy strategies for breast cancer. We report that increased NSC tropism to breast tumor cell lines is strongly correlated with the invasiveness of cancer cells. Interleukin 6 (IL-6) was identified as a major cytokine mediating NSC tropism to invasive breast cancer cells. We show for the first time in a preclinical mouse model of metastatic human breast cancer that NSCs preferentially target tumor metastases in multiple organs, including liver, lung, lymph nodes, and femur, versus the primary intramammary fat pad tumor. For proofof- concept of stem cell-mediated breast cancer therapy, NSCs were genetically modified to secrete rabbit carboxylesterase (rCE), an enzyme that activates the CPT-11 prodrug to SN-38, a potent topoisomerase I inhibitor, to effect tumor-localized chemotherapy. In vitro data demonstrate that exposure of breast cancer cells to conditioned media from rCE-secreting NSCs (NSC.rCE) increased their sensitivity to CPT-11 by 200-fold. In vivo, treatment of tumor- bearing mice with NSC.rCE cells in combination with CPT-11 resulted in reduction of metastatic tumor burden in lung and lymph nodes. These data suggest that NSCmediated enzyme/prodrug therapy may be more effective and less toxic than currently available chemotherapy strategies for breast cancer metastases

Scientific Abstract:
Metastasis to multiple organs is the primary cause of mortality in breast cancer patients. The poor prognosis for patients with metastatic breast cancer and toxic side effects of currently available treatments necessitate the development of effective tumor-selective therapies. Neural stem cells (NSCs) possess inherent tumor tropic properties that enable them to overcome many obstacles of drug delivery that limit effective chemotherapy strategies for breast cancer. We report that increased NSC tropism to breast tumor cell lines is strongly correlated with the invasiveness of cancer cells. Interleukin 6 (IL-6) was identified as a major cytokine mediating NSC tropism to invasive breast cancer cells. We show for the first time in a preclinical mouse model of metastatic human breast cancer that NSCs preferentially target tumor metastases in multiple organs, including liver, lung, lymph nodes, and femur, versus the primary intramammary fat pad tumor. For proof-of-concept of stem cell-mediated breast cancer therapy, NSCs were genetically modified to secrete rabbit carboxylesterase (rCE), an enzyme that activates the CPT-11 prodrug to SN-38, a potent topoisomerase I inhibitor, to effect tumor-localized chemotherapy. In vitro data demonstrate that exposure of breast cancer cells to conditioned media from rCE-secreting NSCs (NSC.rCE) increased their sensitivity to CPT-11 by 200-fold. In vivo, treatment of tumor-bearing mice with NSC.rCE cells in combination with CPT-11 resulted in reduction of metastatic tumor burden in lung and lymph nodes. These data suggest that NSC-mediated enzyme/prodrug therapy may be more effective and less toxic than currently available chemotherapy strategies for breast cancer metastases.